

REMARKS/ARGUMENTS

Reexamination and reconsideration of this Application, withdrawal of the rejections, and formal notification of the allowability of all claims as now presented are earnestly solicited in light of the remarks that follow.

Claim 1 has been amended to recite a method of forming a taxane or precursor or analog thereof from a raw material that comprises the compounds of the previously recited formula. The claim has been amended to include a further description of "X," to recite the formed compounds are in a solid, purified form, and to recite further method steps. Claims 2-12, 62-69, and 101-109 have been amended to harmonize the language thereof with amended claim 1. Support for these amendments can be found throughout the originally filed specification and claims, and more particularly at pages 18-20. Claim 13 has been amended to recite a method of forming a taxane amine or salt, to recite the use of a protic solvent, and to recite further method steps around hydrolysis and isolation of a solid, purified taxane amine or salt. Support for these amendments can be found throughout the specification and claims as originally filed, and particularly at pages 16-18. Claims 34, 70, 79, 80, and 110-112 have been canceled. New claims 113-118 have been added and find support throughout the application as originally filed, particularly at pages 16-20. Claims 1-13, 62-69, 101-109, and 123-118 are pending.

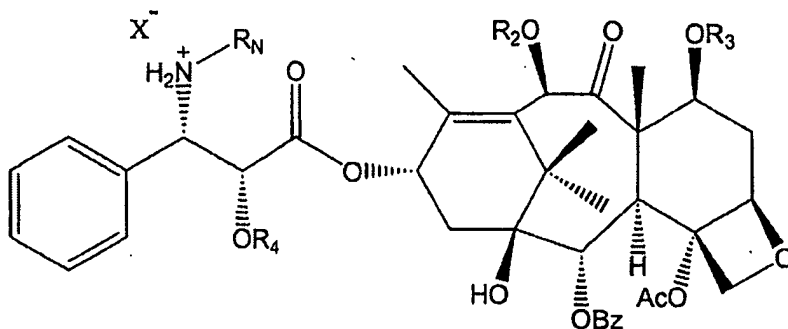
Specification

The Examiner has required amendment of the specification (page 5, second full paragraph) in relation to subject matter incorporated by reference to an unpublished U.S. patent application. The subject matter from the provisional patent application incorporated at page 5 of the present application has now been published as US 2006/0035962. This is the publication of U.S. Application Ser. No. 11/196,950, which claims priority to disclosed provisional application. Applicant submits that the subject matter incorporated by reference is now published in an acceptable form according to 37 CFR 1.57. The noted portion of the specification has been amended to note this chain of reference, including the publication.

Obviousness Rejection

Claims 1-13, 34, 62-70, 79, 80, and 101-112 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over U.S. Patent No. 5,679,807 to Murray et al. and/or U.S. Patent No. 6,448,417 to Sisti et al. Applicant respectfully traverses this rejection.

Claim 1 presently recites a method for forming a taxane or precursor or analog thereof from a raw material, the raw material comprising a compound represented by the formula below:



wherein, R₂ is H, Ac or a protecting group;

R₃ is H, xylosyl or protecting group;

R₄ is H or protecting group;

R_N is H or an alkyl group; and

X= deprotonated sulfuric acid or deprotonated sulfur containing acid;
deprotonated nitric acid or other nitrogen containing acid; deprotonated carboxylic acid, except trifluoro acetic acid; deprotonated phosphoric acid or any phosphorus containing acid; deprotonated tartaric acid; deprotonated p-toluene sulfonic acid; or deprotonated picric acid.

Further, the taxane or precursor or analog thereof is in a solid, purified form. Moreover, the method specifically comprises benzoylating the raw material with a benzoylation solution comprising a benzoylating agent and a buffer such that the pH of the benzoylation solution is about 4 to about 6. Applicant submits that the cited references

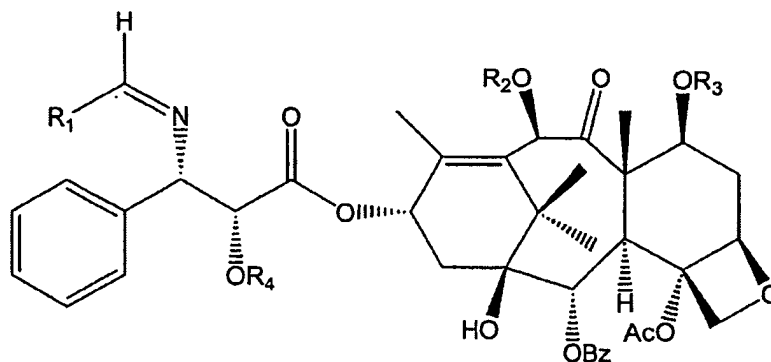
do not disclose or suggest such a method.

As pointed out at page 18 of the present Description (under subheading 7), a taxane amine salt may be converted to a taxane by reaction with benzoyl chloride. However, the Description points out that this is not preferred because of the production of a specific impurity that is difficult to remove in downstream purification steps. According to the present invention, it has been found that formation of this impurity is strongly pH dependant. Thus, the invention overcomes this technical problem by foregoing the use of excess base and instead using a buffer solution, which preferably has a pH of about 7, and which preferably causes the overall reaction solution to have a pH of about 4 to 6. The presently cited references do not disclose or suggest such a method. Rather, Murray et al. generally teach using a base, such as sodium bicarbonate, to effect neutralization. Similarly, Sisti et al. teach the use of potassium carbonate. Murray et al. and Sisti et al. certainly do not teach or suggest the use of a buffer, as presently claimed. Moreover, neither Murray et al. nor Sisti et al. correlate the formation of undesirable impurities with solution pH and thus do not disclose or suggest that impurities can be avoided by foregoing the use of a base and substituting a buffer.

Page 19 of the present Description discloses that benzoylation further causes impurities because of residual benzoyl chlorides present after separation of crude taxane. Claim 113 recites contacting the benzoylation solution with an amine containing compound after the benzoylating reaction is complete. As pointed out on page 19 of the Description, this is an alternative to immediately separating out the crude taxane compound, and it results in the removal of residual benzoyl chlorides and avoids the formation of undesirable impurities. To further avoid formation of impurities, claim 116 recites isolating an organic layer and washing the organic layer with a composition comprising an amine containing compound. Murray et al. and Sisti et al. do not disclose or suggest these specific steps used to avoid formation of impurities. Accordingly, Applicant submits claim 1 and its dependant claims are not obvious over either of the cited documents.

Present claim 13 recites a method of forming a taxane amine or salt comprising the steps following steps:

(i) contacting a taxane imine according to the formula below with a protic solvent;



wherein, R₁ =alkyl, aryl, carbonyl or ether group;

R₂ =H, alkyl, aryl, ester, ether or protecting group;

R₃ =H, alkyl, aryl, ether, ester, xylosyl, or protecting group;

R₄ =H or protecting group;

(ii) contacting the taxane imine with an acid useful to effect hydrolysis of the imine; and

(iii) isolating a solid, purified taxane amine or salt by adding a solvent that is less polar than said protic solvent.

Claim 13 recites a method that results in the isolation of a solid, purified taxane amine or salt. Performing acid hydrolysis using the two claimed solvents achieves this result. The claimed method is not disclosed or suggested by the cited documents and is particularly desirable in that it directly results in a solid, purified taxane salt – without the need to perform any “conventional technical means” to purify an isolated intermediate. Rather, the method of claim 13 uses the combination of a protic solvent to form a solution of the taxane imine, acids that effect hydrolysis, preferably without the formation of impurities, and a specific solvent that is less polar than the protic solvent. By this method, a purified salt is formed without the need for further purification steps.

Neither Murray et al. nor Sisti et al. disclose or suggest that by combining an appropriate acid with a two solvent system of different polarities, a purified taxane salt can be prepared that foregoes the need to perform later purification steps. Accordingly,

Applicant respectfully submits that present claim 13 is not obvious over either of the cited documents.

In light of the foregoing, Applicant respectfully submits the presently rejected claims are not obvious over Murray et al. and/or Sisti et al. Accordingly, Applicant requests reconsideration and withdrawal of the present rejection.

Anticipation

Claims 1-13, 34, 62-70, 79, 80, and 101-112 stand rejected under 35 U.S.C. §103(a) as allegedly being anticipated by U.S. Patent No. 7,220,872 to Johnson et al. Applicant respectfully traverses this rejection.

Applicant directs the Examiner's attention to the previous statements regarding the claimed subject matter and the failure of the art to disclose or suggest the presently claimed methods. Applicant submits the above arguments are equally applicable to the present rejection.

First, in relation to claim 1, Johnson et al. do not disclose or suggest a method for forming a taxane or precursor or analog thereof from a raw material, the raw material comprising the recited salt compound. In particular, Johnson et al. do not disclose, expressly or inherently, benzoylating a raw material with a benzoylation solution comprising a benzoylating agent and a buffer such that the pH of the benzoylation solution is about 4 to about 6.

Second, in relation to claim 13, Johnson et al. do not disclose or suggest a method of forming a taxane amine or salt from an imine compound by using acid hydrolysis in combination with a specific two solvent system. In particular, Johnson et al. do not disclose, expressly or inherently, contacting a taxane imine with a first, protic solvent, performing hydrolysis with an acid, and then isolating a solid, purified taxane amine or salt by adding a second solvent that is specifically less polar than the first solvent.

Since Johnson et al. do not disclose, expressly or inherently, each and every aspect of the present claims, Applicant submits the claims are not anticipated by the cited document. Accordingly, Applicant requests reconsideration and withdrawal of the present rejection.

It is believed that all pending claims are now in condition for immediate allowance. It is requested that the Examiner telephone the undersigned should the Examiner have any comments or suggestions in order to expedite examination of this case.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR §1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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